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Letters to the Editors

Letter to the Editor on "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria"

To the Editor:

We read with interest the article entitled "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria" by Parvizi et al [1]. Our group includes pathologists with subspecialty expertise in hemostasis and thrombosis testing and orthopedic surgeons; we are especially interested in the proposed use of D-dimer in modified scoring criteria for diagnosis of periprosthetic joint infection.

We believe that there are several issues with including D-dimer in the proposed modified scoring criteria. First, the article refers to serum D-dimer; however, the commonly used clinical laboratory assays we are aware of measure D-dimer in patient plasma [2]. Next, the criteria were developed from data contributed by 3 different academic medical centers [1]. Given the variety of D-dimer assay kits that are currently commercially available, it is likely that different centers are using different assays, but the type and laboratory performance characteristics of the assay used in each center are not clearly stated in the article [3,4]. D-dimer assays are not well standardized and the variability among kits may impact whether any individual kit may be used in the proposed criteria. We have seen an example of assay variability making certain D-dimer assays inappropriate for use in the HERDOO2 clinical decision rule, which is designed to identify women with first unprovoked VTE who are at low risk of VTE recurrence and could discontinue anticoagulant therapy [5]. If a laboratory does not know which D-dimer kit was used to create the proposed periprosthetic joint infection criteria, it will not be able to determine whether its D-dimer result can be used in the criteria for clinical decision-making. A clarification of the D-dimer assays used by the participating institution will be helpful to the readers. It is also likely that if a laboratory or practice would like to adopt these criteria, some validation or verification of the local D-dimer assay for this specific indication may be needed. Second, D-dimer may be reported in several different unit magnitudes (eg, ng/mL, μg/L, and others) and there are 2 different unit types (fibrinogen equivalent units [FEU] and D-dimer units [D-DU]) [3,4]. The unit magnitude and type must be included with numeric D-dimer results to allow laboratories to properly interpret and compare the result; however, the D-dimer values included in the article only describe the unit magnitude (ng/mL) [1]. For example, if the proposed threshold for D-dimer as presented by Parvizi et al is 860 ng/mL D-DU, applying this 860 ng/mL D-DU cutoff to a D-dimer result measured in FEU will give false-positive results. The mathematical relationship between the unit types indicates that approximately 2 ng/mL FEU is equal to 1 ng/mL DDU; therefore, a cutoff of 860 ng/mL D-DU would be equivalent to a threshold of 1720 ng/mL FEU. If the proposed threshold represents ng/mL FEU, then applying an 860 ng/mL FEU threshold to results measured in D-DU will give false-negative results (given that the equivalent threshold in D-DU is 430 ng/mL D-DU). Inadequate communication of the specific D-dimer assays appropriate for use in these criteria and of the D-dimer unit type will prevent laboratories from being able to provide appropriate D-dimer testing needed for adoption of these criteria in clinical practice. Furthermore, the observed contribution of D-dimer to the proposed criteria may not hold when one accounts for the effects of D-dimer assay variability.

In conclusion, the issues we identify in the use of D-dimer in proposed scoring criteria for periprosthetic joint infection presented by Parvizi et al result from a well-described root cause, namely the lack of standardization of D-dimer assays. D-dimer assays lack standardization in unit reporting and lack a common calibrator to standardize the varied assays in common clinical use; furthermore, D-dimer assays use over 20 different monoclonal antibodies of differing specificity, further contributing to differences in assay performance [2,3]. Until standardization of D-dimer assays improves, we will continue to see confusion in clinical use and reporting of D-dimer results. Due to lack of standardization, D-dimer assays are currently not interchangeable, and patient results obtained in different laboratories using different D-dimer assays cannot be compared or evaluated for trends. We reiterate that collaboration among regulatory bodies, professional organizations, and reagent manufacturers is necessary to improve standardization and use of D-dimer results and thus enhance the validity of research and subsequently improve patient outcomes [6]. In light of the issues we have highlighted with D-dimer measurement, we find it concerning that the use of D-dimer for diagnosis of periprosthetic joint infection as proposed by Parvizi et al is mentioned in additional more recent publications, which show a similar lack of detail about the D-dimer assays used in the patients studied [7,8]. There is a risk to patients for clinical and surgical mismanagement if D-dimer assays are used in the proposed periprosthetic joint infection criteria given the limitations we outline above.

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Reply to Letter to the Editor Regarding "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria"

In Reply:

We thank you for the informative letter that raises several important issues regarding some of the subtleties involved in using D-dimer as a diagnostic test. The data presented by Moser et al [1] are extremely useful for the orthopedic community and should be taken into consideration when conducting research or using D-dimer in a clinical situation. . The D-dimer assay used in the current study was the HemosIL D-Dimer 500 kit on the ACL TOP instrument, measured on patient plasma. Results are reported in fibrinogen equivalent units (FEUs, ng/mL).

As we all know D-dimer testing has been used in the workup of deep vein thrombosis (DVT) and venous thromboembolism (VTE) for many years. The lack of standardization among the various assays has been a topic of dispute and much discussion and research outside of orthopedics. Although we do not dispute that the various assays and units of reported results are of importance, the question whether a single cut-off value can apply to all (or at least vast majority) remains a valid one. In fact, examining the literature shows that majority of studies use a conventional predetermined cutoff of 500 μg/L to rule out VTE [2–4]. Moreover, an age-adjusted cutoff is now used routinely [5] and all studies that were aimed to validate this cutoff demonstrated a low error rate of <1% regardless to the D-dimer assay used [6–8] suggesting that the choice of assay seems to be of minor importance [9]. In the ADJUSTED-PE study that was published in JAMA, a value of 500 μg/L was regarded as the "conventional" cutoff and despite the fact that 6 different assays were used, this did not affect the utility of age-adjusted D-dimer cutoffs [4]. This information settles some of the major concerns raised by the authors; despite variations in assay, conventional cutoffs for D-dimer are currently successfully used in clinical practice and research.

Although we agree with the authors on the importance of transparency and its relevance in result interpretation, we believe that a cutoff for D-dimer may be generalized in the screening for periprosthetic joint infection (PJI), as it is generalized in workup for DVT/PE. The use of D-dimer in the 2018 definition for PJI was not aimed to make a definite diagnosis but to be used as an adjunct to current commonly used serum markers [10]. Although data for D-dimer were less available compared to other serum tests, the decision to include it was due to the notion that the number of patients with PJI and normal C-reactive

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